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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: McCallester et al. Examiner: S. A. Jiang

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For: EFFERVESCENT COMPOSITIONS COMPRISING BISPHOSPHONATES AND METHODS RELATED THERETO

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents

Washington, DC 20231

Sir:

I, Marshall A. Hayward, Ph.D., hereby make the following declaration:

1. I received a B.Sc. degree from Michigan State University in the year 1977 and a Ph.D. degree from the University of Illinois at Urbana-Champaign in 1983.

2. From 1983 to 1988 I was employed by the company that is now Wyeth as a Principal Scientist in Osteoporosis Research. From 1988 to 1989 I was a Senior Scientist with Johnson and Johnson Health Care Company with responsibilities in wound care research. From 1989 through 1997 I was with the company that is now Glaxo Smith Kline, with responsibilities in technology development and drug delivery, working under several titles and eventually as Director and Vice President, Analgesics Research and Development. From 1997 through 1999, I was with Rhodia Inc. as Director, Business Development. In 2000, I joined Hurley Consulting Associates Ltd. as Vice President, Business Development. I am currently the Chief Scientific Officer of EffRx, Inc., Tequesta, FL, with primary responsibilities in effervescent product development.

3. I have read the subject patent application, the rejections in the Office Action dated June 18, 2003, and the prior art cited against the invention (Katdare et al. '759 and Daifotis et al. '329). I am fully familiar with the field of technology embraced by this patent application and the cited prior art.

4. I have reviewed the results reported in the Röhrich Declaration that is being submitted herewith.

5. Patients now receiving conventional bisphosphonate treatment are routinely instructed to remain upright for about 30 minutes after taking each dose. Even if this regimen is followed, patients often do not tolerate the drug well due to irritation of the esophagus and gastric lining. Damage to the esophagus has been studies and shown to be worse in an acidic environment. (Dobrucali A, *Physiological and morphological effects of alendronate on rabbit esophageal epithelium,* Am J Physiol Gastrointest Liver Physiol. 2002 Sep; 283(3):G576-86.)

6. Bisphosphonate absorption proceeds only after the stomach contents have emptied into the intestine, with negligible absorption occurring in the stomach. Therefore, inclusion of ingredients that have a prokinetic effect on the gastric emptying rate offer an improved method of administration. (see, e.g., Grattan, et al., Eur. J. of Pharm. and Biopharm, 49, 225 – 229 (2000); page 225, col. 2.)

7. The present method for administering bisphosphonates depends on using an effervescent composition having a pH of 4.5 to about 5.5, along with high buffering capacity. This combination helps the stomach to rapidly eject the effervescent solution, while mediating the pH for the time that the drug is in the stomach.

8. One can inhibit the natural stomach acid secretion which occurs when food enters the stomach (a process known as "acid rebound") by selecting a starting pH below about 6. Use of a large quantity of the effervescent system (e.g., 3.5 to about 6 grams total weight) helps mediate the stomach pH at the chosen pH due to its high buffering capacity, and provides, as a separate benefit, vigorous effervescence, which helps the stomach eject the solution quickly. Together these effects reduce the irritation potential of the bisphosphonates.

9. The table of the Röhrich Declaration shows that three of the Katdare et al. formulas have a pH of 6.1 or more and thus would tend to promote acid secretion by the stomach though the acid rebound process. Such formulations are not optimal for administering bisphosphonates because the buffering system must cope with more acid secretion.

10. The Röhrich Declaration shows that Example 1 of Katdare et al. has a pH of 4.3, but that its acid neutralizing capacity (ANC) is quite low - 2.95 mEq of

acid per dose. As a point of reference, one can compare this value to an ordinary antacid tablet, which must have an ANC of 5 mEq or more per dose to be considered an antacid. (USP Official Monographs (302); attached hereto). While this USP standard was developed specifically for calcium carbonate tablets, it indicates that Example 1 of Katdare has very little buffering capacity. For this reason I conclude that it would not mediate the stomach pH significantly, or provide optimal protection from irritation by the bisphosphonate.

11. The table of the Röhrich Declaration also shows that the Katdare et al. Examples have total weights ranging from 1.1 to about 2.5 grams, compared to 3.5 to about 6 grams in the present invention. Such small amounts of effervescing components in Katdare et al. would tend to not create as vigorous bubbling action and not promote as rapid ejection of the solution from the stomach. Such solutions would be more prone to cause irritation by the bisphosphonate.

12. In summary, Katdare et al. teaches that bisphosphonates can be administered in effervescent solution by dissolving them in any given effervescent system. But it does not guide one to select a starting pH in the range of 4.5 to about 5.5 to minimize acid rebound, or indicate that a system with high buffering capacity and effervescent action would promote ejection of the solution from the stomach. Katedare et al. also does not disclose a reason to select a total weight of from 3.5 to about 6 grams of the solid components.

13. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both,

under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 15 December 2003 By: _____

Marshall A. Hayward, Ph.D.

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Calcium Carbonate Tablets

» Calcium Carbonate Tablets contain not less than 92.5 percent and not more than 107.5 percent of the labeled amount of calcium carbonate ($CaCO_3$).

Packaging and storage—Preserve in well-closed containers.

Labeling—Label it to indicate whether it is for use as an antacid, or as a dietary supplement, or both.

Identification—The addition of 6 N acetic acid to the Tablets produces effervescence, and the resulting solution, after being boiled to expel carbon dioxide and neutralized with 6 N ammonium hydroxide, meets the requirements of the tests for *Calcium* ⟨191⟩.

Dissolution ⟨711⟩—For Tablets labeled for any indication other than, or in addition to, antacid use.

Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 2: 75 rpm.

Time: 30 minutes.

Determine the amount of $CaCO_3$ dissolved by employing the following method.

Lanthanum chloride solution, 5%—Prepare a solution of lanthanum chloride in 0.1 N hydrochloric acid having a concentration of about 50 mg per mL.

Blank—Pipet 25 mL of *Lanthanum chloride solution, 5%* into a 250-mL volumetric flask, dilute with 0.1 N hydrochloric acid to volume, and mix.

Standard stock solution—Dissolve an accurately weighed quantity of calcium carbonate in 0.1 N hydrochloric acid, and dilute quantitatively, and stepwise if necessary, with 0.1 N hydrochloric acid to obtain a solution having a known concentration of about 100 µg of calcium per mL.

Standard solutions—Into four 100-mL volumetric flasks, each containing 10.0 mL of *Lanthanum chloride solution, 5%*, separately pipet 3-, 4-, 5-, and 6-mL portions of *Standard stock solution*. Dilute each with 0.1 N hydrochloric acid to volume, and mix to obtain *Standard solutions* having known concentrations of about 3, 4, 5, and 6 µg of calcium per mL, respectively.

Test solution—Filter a portion of the solution under test. Pipet a volume of the filtrate, estimated to contain 1 mg of calcium, into a 250-mL volumetric flask, add 25.0 mL of *Lanthanum chloride solution, 5%*, dilute with 0.1 N hydrochloric acid to volume, and mix.

Procedure—Concomitantly determine the absorbances of the *Standard solutions* and the *Test solution* at the calcium emission wavelength of 422.8 nm, with a suitable atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩), equipped with a calcium hollow-cathode lamp and an air-acetylene flame, against the *Blank*. Construct a standard curve by plotting absorbances versus calcium concentrations of the *Standard solutions*, then from it obtain the concentration, C, in µg of calcium per mL, of the *Test solution*, and calculate the quantity, in mg, of $CaCO_3$ dissolved by the formula:

$$(100.09/40.08)(225C/v),$$

in which 100.09 is the molecular weight of calcium carbonate; 40.08 is the atomic weight of calcium; and v is the volume of the filtrate taken to prepare the *Test solution*.

Tolerances—Not less than 75% (Q) of the labeled amount of $CaCO_3$ is dissolved in 30 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Acid-neutralizing capacity ⟨301⟩—Where Tablets are labeled for antacid use, not less than 5 mEq of acid is consumed by the minimum single dose recommended in the labeling, and not less than the number of mEq calculated by the formula:

$$0.9(0.02C),$$

in which 0.02 is the theoretical acid-neutralizing capacity, in mEq, of $CaCO_3$; and C is the quantity, in mg, of $CaCO_3$ in the specimen tested, based on the labeled quantity.

Assay—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 200 mg of calcium carbonate, to a suitable crucible, and ignite to constant weight. Cool the crucible, add 10 mL of water, and dissolve the residue by adding sufficient 3 N hydrochloric acid, dropwise, to achieve complete solution. Transfer the solution completely to a suitable container, dilute with water to 150 mL, add 15 mL of 1 N sodium hydroxide and 300 mg of hydroxy naphthol blue, and titrate with 0.05 M edetate disodium VS until the solution is deep blue. Each mL of 0.05 M edetate disodium is equivalent to 5.004 mg of calcium carbonate ($CaCO_3$).

Calcium Carbonate and Magnesia Tablets

» Calcium Carbonate and Magnesia Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of calcium carbonate ($CaCO_3$) and not less than 90.0 percent and not more than 115.0 percent of the labeled amount of magnesium hydroxide [$Mg(OH)_2$].

Packaging and storage—Preserve in well-closed containers.

Labeling—Label the Tablets to indicate that they are to be chewed before being swallowed.

Identification—

A: The addition of 3 N hydrochloric acid to the Tablets produces effervescence, and the resulting solution, after being boiled to expel carbon dioxide and neutralized with 6 N ammonium hydroxide, meets the requirements of the tests for *Calcium* ⟨191⟩.

B: Heat 2 Tablets in 20 mL of 1 N sulfuric acid. Cool, add 20 mL of alcohol, mix, and allow to stand for 30 minutes. Filter this solution and add 2 mL of 1 N hydrochloric acid to the filtrate: this solution meets the requirements of the tests for *Magnesium* ⟨191⟩.

Uniformity of dosage units ⟨905⟩: meet the requirements for *Weight Variation* with respect to calcium carbonate and to magnesium hydroxide.

Acid-neutralizing capacity ⟨301⟩—Not less than 5 mEq of acid is consumed by the minimum single dose recommended in the labeling, and not less than the number of mEq calculated by the formula:

$$0.8(0.0343M) + 0.9(0.02C),$$

in which 0.0343 and 0.02 are the theoretical acid-neutralizing capacities, in mEq, of $Mg(OH)_2$ and $CaCO_3$, respectively; and M and C are the respective quantities, in mg, of $Mg(OH)_2$ and $CaCO_3$ in the specimen tested, based on the labeled quantities.

Assay for calcium carbonate—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 400 mg of calcium carbonate, to a beaker with 25 mL of water, and add 40 mL of 1 N hydrochloric acid. Heat on a steam bath for 30 minutes, allow to cool, transfer to a 100-mL volumetric flask with the aid of water, dilute with water to volume, mix, and filter. Transfer 20.0 mL of the filtrate to a suitable container, dilute with water to 100 mL, add 30 mL of 1 N sodium hydroxide, 4 mL of triethanolamine, and 100 mg of hydroxy naphthol blue, and titrate with 0.05 M edetate disodium VS until the solution is deep blue in color. Each mL of 0.05 M edetate disodium is equivalent to 5.004 mg of calcium carbonate ($CaCO_3$).

Assay for magnesium hydroxide—Transfer an accurately measured portion of the filtrate remaining from the *Assay for calcium carbonate*, equivalent to about 120 mg of calcium carbonate and magnesium hydroxide combined, to a suitable container, dilute with water to 100 mL, add 10 mL of ammonia–ammonium chloride buffer TS, 4 mL of triethanolamine, and 0.3 mL of eriochrome black TS, and titrate with 0.05 M edetate disodium VS to a blue endpoint. The volume, in mL, of 0.05 M edetate disodium consumed, less the volume of 0.05 M edetate disodium corresponding to the content of calcium carbonate in the volume, in mL, of the filtrate taken, represents the volume, in mL, of 0.05 M edetate disodium equivalent to the quantity of magnesium hydroxide present. Each mL of 0.05 M edetate disodium is equivalent to 2.916 mg of $Mg(OH)_2$.